Neuropharmacology 66 (2013) 31–39

Contents lists available at SciVerse ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

Invited review

Role of presynaptic metabotropic glutamate receptors in the induction of long-term synaptic plasticity of vesicular release

Chirag Upreti [a], Xiao-lei Zhang [a], Simon Alford [b], Patric K. Stanton [a,c,*]

[a] Department of Cell Biology & Anatomy, New York Medical College, Valhalla, NY 10595, USA
[b] Department of Biological Sciences, University of Illinois at Chicago, Chicago, IL 60607, USA
[c] Department of Neurology, New York Medical College, Valhalla, NY 10595, USA

ARTICLE INFO

Article history:
Received 13 February 2012
Received in revised form
7 May 2012
Accepted 9 May 2012

Keywords:
Group II metabotropic glutamate receptors
G protein-coupled receptors
Gαi
Gβγ
Long-term synaptic depression
SNAP-25
SNARE protein
Synaptic plasticity
Vesicular release

ABSTRACT

While postsynaptic ionotropic and metabotropic glutamate receptors have received the lions share of attention in studies of long-term activity-dependent synaptic plasticity, it is becoming clear that presynaptic metabotropic glutamate receptors play critical roles in both short-term and long-term plasticity of vesicular transmitter release, and that they act both at the level of voltage-dependent calcium channels and directly on proteins of the vesicular release machinery. Activation of G protein-coupled receptors can transiently inhibit vesicular release through the release of Gβγ which binds to both voltage-dependent calcium channels to reduce calcium influx, and directly to the C-terminus region of the SNARE protein SNAP-25. Our recent work has revealed that the binding of Gβγ to SNAP-25 is necessary, but not sufficient, to elicit long-term depression (LTD) of vesicular glutamate release, and that the concomitant release of $G\alpha_i$ and the second messenger nitric oxide are also necessary steps in the presynaptic LTD cascade. Here, we review the current state of knowledge of the molecular steps mediating short-term and long-term plasticity of vesicular release at glutamatergic synapses, and the many gaps that remain to be addressed.

This article is part of a Special Issue entitled 'Metabotropic Glutamate Receptors'.

1. Introduction

Neurons communicate with one another via chemical messengers called neurotransmitters. Synaptic transmission, i.e. the process of transmitting electrical impulses from one neuron to the other via a chemical intermediate, is crucial for the normal function of a neural network, and perturbations of these junctions have been correlated with many neurological diseases, such as Alzheimer's, schizophrenia and Parkinson's (Cook and Leuchter, 1996; Huang et al., 2011; Nathan et al., 2011). Synapse strength can be bi-directionally modified in an activity-dependent manner, and these changes can be brief or persistent. William James (1890), at a time when the neuron doctrine and the role of synapses in intercellular communication had yet to emerge, postulated that long-lasting alterations in the strength of connections between excitable elements of the brain could be a way in which memories are stored, an early "connectionist" view that is as current over a century later.

Homosynaptic long-term potentiation (LTP) is a persistent, synapse-specific strengthening of synaptic transmission induced by brief bursts of high frequency synaptic activity (100–200 Hz), whereas long-term synaptic depression (LTD) is weakening of synaptic strength, usually triggered by low frequency activation (1–5 Hz) for prolonged periods (10–15 min). These persistent changes in synaptic strength are widely considered to be leading candidates for cellular mechanisms of memory storage (Bliss et al., 2006; Pastalkova et al., 2006; Whitlock et al., 2006). Glutamate serves as the main excitatory neurotransmitter in the central nervous system and uses a myriad of receptor subtypes to activate ionic channels to change membrane potential, and G protein-coupled receptors to initiate downstream signal transduction. The glutamate receptor family can be divided into two types: **a)** fast, ionotropic glutamate receptors that include 2-amino-3-(5-methyl-3-oxo-1,2- oxazol-4-yl)propanoic acid (AMPA), N-Methyl-D-aspartate (NMDA) and kainate receptors (Madden, 2002) and **b)** G-protein coupled metabotropic receptors that act via second messenger cascades (mGluR) (Nicoletti et al., 2011; Niswender and Conn, 2010; Pinheiro and Mulle, 2008). The mGluR superfamily can be divided into eight different receptor subtypes on the bases of their sequence homology, pharmacologic properties and activation

* Corresponding author. Department of Cell Biology & Anatomy, New York Medical College, Valhalla, NY 10595, USA. Tel.: +1 914 594 4883; fax: +1 914 594 4653.
E-mail address: patric_stanton@nymc.edu (P.K. Stanton).

0028-3908/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
doi:10.1016/j.neuropharm.2012.05.004

of downstream signal transduction pathways (Conn and Pin, 1997). Group I metabotropic receptors consist of $mGluR_1$ and $mGluR_5$, which are primarily expressed postsynaptically with a somatodendritic distribution. These receptors are selectively activated by 3,5-dihydroxyphenyl-glycine (DHPG) and coupled to heterotrimeric G_q proteins that stimulate PLC-β to produce the intracellular messengers inositol trisphosphate (IP_3) and diacylglycerol (DAG) through phosphatidylinositol hydrolysis. IP_3 triggers release of calcium from intracellular endoplasmic reticulum calcium stores (Fagni et al., 2000), while DAG recruits protein kinase C (PKC) to the membrane and activates it (Ferraguti et al., 2008; Houamed et al., 1991; Masu et al., 1991), resulting in enhanced excitability of hippocampal neurons via modulation of Ca^{2+}, K^+ and non-selective cation channels, as well as many longer term effects mediated by serine–threonine phosphorylation of numerous target proteins.

Group II mGluRs ($mGluR_2$ and $mGluR_3$), and group III mGluRs ($mGluR_4$, $mGluR_7$ and $mGluR_8$) are coupled to $G_{i/o}$ proteins that inhibit adenylate cyclase, preventing the formation of cyclic adenosine 3′5′-monophosphate (cAMP). These receptors are expressed both presynaptically and postsynaptically. Presynaptically, their activation can decrease transmitter release by reducing voltage-dependent Ca^{2+} channel conductance through direct binding of Gβγ to the channel, by interfering directly with the presynaptic release apparatus, or both (Anwyl, 1999; Cartmell and Schoepp, 2000). In the hippocampus, group II mGluRs are believed to be localized primarily in presynaptic terminals, while group III mGluR are located in or near presynaptic active zones (Shigemoto et al., 1997). While these mGluRs are perfectly positioned to regulate synaptic transmission, the role of presynaptic mGluR in persistent plasticity of vesicular transmitter release is still relatively underexplored.

2. Presynaptic component of LTD of synaptic transmission

Homosynaptic LTD is an input-specific, long-lasting reduction in synaptic strength induced by prolonged low-frequency stimulation that has been observed at a variety of glutamatergic synapses in the hippocampus (Bear and Abraham, 1996), neocortex and other brain regions (Collingridge et al., 2010). Homosynaptic, associative LTD can be evoked at a synaptic input that is activated out of phase with a second bursting input that converges on the same neuron (Chattarji et al., 1989; Stanton and Sejnowski, 1989), or temporally mismatching presynaptic and postsynaptic activation to mimic such activity (Debanne et al., 1994; Stanton and Sejnowski, 1989). The N-methyl-D-aspartate subtype of glutamate receptor (NMDAR) has been found to be essential for the induction of some forms of long-term synaptic plasticity because a) it gates the influx of Ca^{2+} and b) its voltage-dependent Mg^{2+} channel block allows the NMDAR to detect the level of coincident pre- and post-synaptic activity at individual synapses (Yuste et al., 1999). NMDAR-gated Ca^{2+} influx leads to the downstream activation of kinases and phosphatases required for inducing LTP and/or LTD in frequency-dependent patterns that elicit differing levels of [Ca^{2+}] increase in dendritic spines. Prolonged stimulation of Schaffer collateral–CA1 synapses at low frequencies (LFS: 1–5 Hz for 10–15 min) elicits a form of LTD (LFS-induced LTD) whose induction is blocked by the NMDAR-selective antagonist D-AP5 (Dudek and Bear, 1992; Mulkey et al., 1993). This stimulation has been suggested to elicit LTD, rather than LTP, because the smaller amplitude and slower rate of postsynaptic [Ca^{2+}] increase selectively activates the high affinity calcium sensitive phophatases calcineurin (PP2B) and PP1, that mediate postsynaptic changes resulting in LTD (Collingridge et al., 2010; Lisman, 1989; Mulkey et al., 1993). This hypothesis is supported by studies showing that inhibition of PP1/PP2A (Mulkey et al., 1993), or of PP2B (Mulkey et al., 1994), blocks the induction of LTD at Schaffer collateral–CA1 synapses. Postsynaptically, calcineurin dephosphorylates and inactivates inhibitor-1 (Mulkey et al., 1994), leading to activation of PP1, which dephosphorylates AMPAR GluR1 subunits at serine-845, thereby both decreasing AMPAR open probability (Lee et al., 1998) and triggering AMPAR internalization (Beattie et al., 2000; Ehlers, 2000). PP1 can also regulate gene expression via the dephosphorylation and inactivation of the transcriptional factor cAMP response element-binding protein (CREB) (Bito et al., 1996; Deisseroth et al., 1996; Hagiwara et al., 1992), preventing activity-dependent expression of early genes such as c-fos, BDNF and Arc, all found to promote LTP (Barco et al., 2005). Additional mechanisms involved in the postsynaptic induction and expression of a significant component of LTD have been addressed in previous reviews and the reader is referred to them for these considerations (Collingridge et al., 2010; Kessels and Malinow, 2009; Poschel and Stanton, 2007).

Calcineurin can also dephosphorylate presynaptic proteins such as synapsin I (Chi et al., 2003; Jovanovic et al., 2001), whose dephosphorylated state is associated with reduced neurotransmitter release through decreasing the size of the readily-releasable vesicle pool (RRP) (Bykhovskaia, 2011; Hilfiker et al., 1999). Activation of NMDAR (Stanton et al., 2003; Zhang et al., 2006), group I (Zakharenko et al., 2002) and group II (Santschi et al., 2006) mGluRs have all been shown to play roles in a presynaptic component of LFS-induced LTD at Schaffer collateral synapses. This presynaptic component of LTD appears to require a retrograde, diffusible intercellular messenger (Bolshakov and Siegelbaum, 1994; Stanton et al., 2003), perhaps arachidonic acid (Bolshakov and Siegelbaum, 1995) and/or nitric oxide (NO) (Stanton et al., 2003; Zhang et al., 2006), generated in the postsynaptic neuron. Retrograde messengers such as NO are membrane permeable, rapidly diffusible gaseous messenger that can diffuse from the postsynaptic compartment to presynaptic terminals within a small three-dimensional volume ($\leq$50 μm^3; Wood and Garthwaite, 1994). A principal physiological enzyme target of NO is soluble guanylate cyclase (Southam and Garthwaite, 1993) and studies have shown that NO mediated elevation of presynaptic [cyclic GMP] requires release of Ca^{2+} from ryanodine-sensitive intracellular stores via the second-messenger cyclic ADP ribose, and that this cascade is a key component of the induction of stimulus-evoked LTD at Schaffer collateral–CA1 synapses (Gage et al., 1997; Izumi and Zorumski, 1993; Reyes-Harde et al., 1999).

At dentate granule cell mossy fiber-CA3 synapses, it is generally agreed that, like LTP, LTD induced by electrical stimulation leads to a largely presynaptically expressed form of LTD. A low frequency stimulus train of 1–2 Hz for 10–15 min can induce LTD at mossy fiber synapses (Kobayashi et al., 1996; Nicholls et al., 2006). This form of LTD depends on the presynaptic G-protein coupled receptors (GPCR) mGluR2 and A1 adenosine receptors, which, upon activation, release Gα subunits that inhibit adenylate cyclase (Kobayashi et al., 1996; Nicholls et al., 2006) and reduce activity of the cAMP-PKA pathway (Tzounopoulos et al., 1998).

2.1. Role of G-protein coupled receptors and $G\alpha_{i2}$ in presynaptic LTD

Studies have shown that inhibition of PKA can augment the magnitude of LTD induced by a subthreshold low-frequency stimulus train (1 Hz/400 s; (Santschi et al., 1999)), and that pairing inhibition of PKA with production of cGMP induces a robust form of chemical LTD (CLTD) with a presynaptic locus of expression requiring activation of cyclic GMP-dependent protein kinase (PKG; Santschi et al., 1999). These studies also found that presynaptic GPCRs such as A1 adenosine receptors and group II mGluRs can supply adenylate cyclase inhibition necessary for induction of LTD (Santschi et al., 1999). Indeed, simultaneous activation of A1